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CASE REPORT

Dentatorubral-pallidoluysian atrophy in two Chinese families in Hong Kong

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We report on two Hong Kong Chinese families with dentatorubral-pallidoluysian atrophy. Two children in one family presented with progressive myoclonic epilepsy syndrome, and two children in the other family presented with ataxochoreo-athetoid symptoms. Early-onset childhood dentatorubral-pallidoluysian atrophy involved mental retardation, whereas myoclonic epilepsy was the predominant complaint in later-onset childhood version of the disease. Aspiration pneumonia was common in the late stage of disease. Dentatorubral-pallidoluysian atrophy is an autosomal dominant condition attributed to CAG trinucleotide repeats in the dentatorubral-pallidoluysian atrophy gene. The four children in this series had 63 to 79 CAG repeats. The expanded allele was inherited from the father in both families. One father had 54 CAG repeats and was asymptomatic; the other had 66 repeats and had an unsteady gait. Because the radiological, electroencephalographic, and electrophysiological findings were non-specific, we suggest that *DRPLA* gene testing should be performed in any child presenting with a variable combination of myoclonic epilepsy, mental retardation or developmental regression, and ataxochoreo-athetosis.

本文報告兩宗香港華人家庭的成員患上齒狀核紅核蒼白球丘腦小體萎縮的病例。在其中一個家庭，兩名兒童出現日趨嚴重的肌陣攣癲癇，另一個家庭的兩名兒童則出現共濟失調、舞蹈症及徐動症狀。早發的兒童期齒狀核紅核蒼白球丘腦小體萎縮患者，會出現智力低下的情況；而遲發者最常見的症狀為肌陣攣癲癇。呼吸性肺炎在患病後期頗為普遍。齒狀核紅核蒼白球丘腦小體萎縮是一種常染色體顯性遺傳病，由齒狀核紅核蒼白球丘腦小體萎縮症基因裡發生CAG三核苷酸重複而造成。四名病童的CAG重複擴展數目由63至79不等，擴展的等位基因都是從父親遺傳而來的。其中一名父親的CAG擴展數目為54，他並無任何徵狀；另外一名父親的CAG擴展數目為66，他有步態不穩的情況。由於患者的放射學、腦電圖及電子生理檢查結果並不具體，我們建議假如兒童出現肌陣攣癲癇、智力低下、發展退化、共濟失調、舞蹈症或徐動症狀等其中兩種或以上病徵，應當接受齒狀核紅核蒼白球丘腦小體萎縮症基因的測試。

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Introduction

Dentatorubral-pallidoluysian atrophy (DRPLA) is a rare neurodegenerative disease. It has been described since 1958 but the underlying genetic defect of a repeated CAG trinucleotide sequence was first documented in 1993.[1,2] We report the clinical, radiological, electro-encephalographic, electrophysiological, and genetic findings of two Hong Kong Chinese families with DRPLA.

Case reports

Family 1

A 16-year-old girl (family 1, case 1) presented to the Alice Ho Miu Ling Nethersole Hospital in June 2002 with an 1-year history of myoclonic jerks of the head and upper limbs. She had had learning difficulties, deterioration in writing ability, and short-term memory problems since the age of 10 years. Investigations showed

a normal complete blood picture and erythrocyte sedimentation rate, as well as normal liver, kidney, and thyroid function, lactate level, ceruloplasmin level, viral test results, anti–double stranded DNA antibody level, and urine metabolic screening. Magnetic resonance imaging (MRI) of the brain gave normal results. The brainstem auditory–evoked potential (BAEP) showed normal peak latencies, but increased I-III interpeak latencies beyond three standard deviations (SDs), and decreased III-V interpeak latencies beyond two SDs. The pure-tone audiogram and tympanogram were normal. The pattern visual–evoked potential (PVEP) and ophthalmological examination results were normal. Somatosensory-evoked potentials (SEPs) of the median and posterior tibial nerves were also normal. The electroencephalogram (EEG) showed very frequent spike and polyspike wave activities, and no abnormal response to slow-rate photic stimulation. Developmental assessment showed mild-grade mental retardation.

Family history revealed that the patient's younger brother (family 1, case 2) was suspected to have neuronal ceroid lipofuscinosis, but the diagnosis could not be confirmed pathologically. He presented to another hospital at the age of 2 years in 1990. The patient's speech development was delayed, he was hyperactive, and he had mild mental retardation. He had had intractable epilepsy since the age of 5 years, and his seizures included generalised tonic-clonic, atonic, and myoclonic types. His condition had regressed gradually, with the development of tic-like movements and extensor spasms, and it deteriorated rapidly since the age of 9 years. At 11 years, mental retardation was severe; he could not speak, required nasogastric tube feeding, became double incontinent, and was bed-ridden. The child also had recurrent aspiration pneumonia. Extensive investigations during the past decade—including blood and urine metabolic screening, electron microscopic examination of blood, conjunctival biopsy, muscle biopsy, and skin biopsy from armpit—gave negative results. However, MRI of the brain showed cerebellar atrophy, and EEG showed epileptic activity—initially focal and later multifocal sharp and spike waves with slowing background activity. There was marked photo-paroxysmal response to photic stimulation at 4 Hz. The BAEP at the age 8 years showed I-III latencies of the right ear that were prolonged beyond two SDs. Flash visual–evoked potential (FVEP) at age 11 years showed an enlarged amplitude of 40 to 60 µV (reference range, 2-10 µV) and delayed latencies beyond two SDs. Ophthalmological assessment yielded normal results. The SEP of the median nerves at age 11 years was normal. The karyotype was normal. The parents were non-consanguineous, and there was no evidence of Japanese ancestry. One sibling had died of birth asphyxia.

In view of the clinical diagnosis of progressive myoclonic epilepsy syndrome in the sister and the familial nature of degenerative problems in both children, we performed genetic studies on genomic DNA samples of members of the family. Both children carried a heterozygous CAG repeat in exon 5 of the *DRPLA* gene: 71 CAG repeats in the gene from the sister and 79 in that of the brother. The brother's result was independently reported by another laboratory. The expanded *DRPLA* allele was subsequently found to be inherited from the father (family 1, case 3). However, his allele contained only 66 CAG repeats. He had a relatively late onset of symptoms, at 42 years, in the form of an unsteady gait.

Family 2
A five-year-old girl (family 2, case 1) presented to the Queen Elizabeth Hospital at the age of 5 years in 1995, because of frequent falls, marked axial ataxia, scanning speech, and intractable myoclonic seizures. She also showed mildly delayed development in speech and fine motor skills. Physical examination showed brisk tendon jerks and marked truncal ataxia. Her condition deteriorated when she was 15 years old, and she lost the ability to walk at 16. She also developed repeated aspiration pneumonia.

The patient's younger brother (family 2, case 2) had had neonatal convulsions associated with hypoxic-ischaemic encephalopathy. He also had early developmental delay, choreo-athetosis of the limbs, and orofacial dyskinesia. He later developed intractable myoclonic epilepsy and eyelid myoclonia. He had only a few echolalia-like utterances and turned mute at the age of 10. At 11 years, he had a prominent tremor of his upper limbs and his general condition started to regress. He had periodic aspiration pneumonia that required gastrostomy and fundoplication. He died at age 12 years.

Tests had been done over the past few years before the younger child died. The younger brother had had normal results from blood and urine metabolism tests. Both siblings could not comply with EEG, MRI, and evoked potential studies. The family was suspected to have spinocerebellar degeneration. Genetic testing showed that both children carried a heterozygous CAG repeat in the *DRPLA* gene. The brother's expanded allele contained 67 CAG repeats and the elder sister's 63 CAG repeats. The expanded allele was inherited from the father (family 2, case 3), whose allele contained only 54 CAG repeats; he remained asymptomatic at age 50 years.

Discussion

Although DRPLA is more common in Japan than in other countries, with an estimated prevalence of 1.1 per 1 million population, there are increasing sporadic reports of DRPLA in non-Japanese patients.[3-6] It remains to be verified whether the prevalence among Chinese populations is lower than that among Japanese populations. To the best of our knowledge, this article is the first to report on the patients of DRPLA in Hong Kong. In four children and one adult, diagnoses were made just within 1 year when molecular testing of DRPLA became available in Hong

Kong. Assuming that the population of Hong Kong is about 6.8 million, we estimate that the minimum prevalence of DRPLA in Hong Kong is 0.74 per 1 million population. As the awareness of the disorder increases among physicians, we expect that more cases will be diagnosed.

As an autosomal dominant disorder, DRPLA is attributed to a repeated CAG trinucleotide sequence in exon 5 of the *DRPLA* gene on chromosome 12p13.[7] This stretch of CAG trinucleotide repeat is highly polymorphic and codes for a polyglutamine stretch of amino acids. People normally have six to 35 CAG repeats, whereas patients with DRPLA have more than 49 repeats. The age of onset and the severity of the disease are correlated to the number of repeats: patients with more repeats generally have an earlier onset and more severe symptoms. This association has been illustrated by the cases in the two families reported in this article.

This CAG trinucleotide repeat is meiotically unstable and further expands on transmission to the next generation, thereby resulting in the genetic phenomenon of antici-pation. The instability is more marked during paternal transmission, and accounts for the large intergenerational difference in the age of onset and severity within the two families described in this case report. Furthermore, the younger siblings in both families were found to have more CAG repeats than their older siblings. This difference may be explained by the combined effect of advancing paternal age and meiotic instability of the CAG repeats. However, more families need to be studied before we can conclude that this birth-order effect, which is also present in other CAG trinucleotide repeat expansion disorders, is a consistent feature in DRPLA.[8]

Clinically, patients with adult-onset DRPLA usually present with pseudo-Huntington symptoms characterised by chorea, cognitive dysfunction, and psychiatric symptoms. Some patients may present with ataxochoreo-athetoid symptoms characterised by progressive ataxia, choreo-athetosis, and dementia. On the other hand, presenting symptoms in childhood-onset DRPLA include myoclonus, epilepsy, and mental regression.[9] The presence of ataxochoreo-athetoid symptoms in childhood-onset DRPLA in the second family in this report suggests that the different forms of DRPLA might overlap.

There were two new observations from our case series. Firstly, mental retardation seemed to be the presenting feature in early-onset childhood DRPLA, whereas myoclonic epilepsy was the predominant complaint in later-onset childhood DRPLA. Both younger siblings in the two families presented early with mental retardation, followed by the development of intractable seizures. On the other hand, the elder siblings had later onsets of disease and presented with myoclonic epilepsy. Mental retardation was not severe initially. Developmental regression in the children became obvious at a much later stage. Secondly, feeding problems and aspiration pneumonia seemed to be the common final outcome for childhood DRPLA. Three of the four children in our series had aspiration pneumonia, which is secondary to feeding problem.

The usual characteristic MRI findings in adult-onset DRPLA include atrophy of brainstem tegmentum; cerebellar atrophy, including that of the dentate nuclei; and periventricular or deep white-matter hyperintensity on T2-weighted images.[10] In childhood-onset DRPLA, MRI findings are more variable.[10,11] Few studies on the EEG or electrophysiological findings in patients with DRPLA have been reported.[12-15] Epileptic EEG activity might be present, but there is no characteristic feature.[12-13] Reduced or absent brainstem component or delayed latencies of BAEP, reduced or absent cortical component or delayed latencies of SEP, and enlarged amplitudes or shortened latencies of FVEP have been reported.[14,15] The neuro-imaging and EEG findings in the first family of our series were consistent with those already published, but their electrophysiological findings were slightly different. Their BAEP results showed prolonged I-III latencies. However, the absolute latencies remained within the normal limits. Their SEPs were normal. The younger brother (family 1, case 2) had an abnormal FVEP but the sister (family 1, case 1) had a normal PVEP. The evoked responses in the elder sister should be followed up longitudinally to find whether the responses might change with disease progression.

Conclusion

Dentatorubral-pallidoluysian atrophy is increasingly being diagnosed because of advancements in medical genetics and the availability of molecular testing. Clinical features in childhood-onset DRPLA include a variable combination of myoclonic epilepsy, mental retardation or developmental regression, and ataxochoreo-athetosis. Neuro-imaging, electroencephalographic, and electrophysiological ab-normalities may be detected. Nevertheless, DNA analysis is crucial to the diagnosis.

Acknowledgements

References

1. Smith JK, Conda VE, Malamud N. Unusual form of cerebellar ataxia: combined dentato-rubral and pallido-luysian degeneration. Neurology 1958;8:205-9.
2. Li SH, McInnis MG, Margolis RL, Antonarakis SE, Ross CA. Novel triplet repeat containing genes in human brain: cloning, expression, and length polymorphisms. Genomics 1993;16:572-9.
3. Hirayama K, Takayanagi T, Nakamura R, et al. Spinocerebellar degenerations in Japan: a nationwide epidemiological and clinical study. Acta Neurol Scand Suppl 1994;153:1-22.

4. Munoz E, Mila M, Sanchez A, et al. Dentatorubropallidoluysian atrophy in a spanish family: a clinical, radiological, pathological, and genetic study. J Neurol Neurosurg Psychiatry 1999;67:811-4.

5. Norremolle A, Nielsen JE, Sorensen SA, Hasholt L. Elongated CAG repeats of the B37 gene in a Danish family with dentato-rubo-pallido-luysian atrophy. Hum Genet 1995;95:313-8.

6. Lee IH, Soong BW, Lu YC, Chang YC. Dentatorubropallidoluysian atrophy in Chinese. Arch Neurol 2001;58:1905-8.

7. Ikeuchi T, Koide R, Onodera O, et al. Dentatorubral-pallidoluysian atrophy (DRPLA). Molecular basis for wide clinical features of DRPLA. Clin Neurosci 1995;3:23-7.

8. Saleem Q, Choudhry S, Mukerji M, et al. Molecular analysis of autosomal dominant hereditary ataxias in the Indian population: high frequency of SCA2 and evidence for a common founder mutation. Hum Genet 2000;106:179-87.

9. Hirayama K, Iizuka R, Maehara K, et al. Clinicopathological study of dentatorubro-pallidoluysian atrophy. Part 1. Its clinical form and analysis of symptomatology. Shinkei Kenkyu no Shinpo 1981;25:725-36.

10. Miyazaki M, Kato T, Hashimoto T, Harada M, Kondo I, Kuroda Y. MR of childhood-onset dentatorubral-pallidoluysian atrophy. AJNR Am J Neuroradiol 1995;16:1834-6.

11. Koide R, Onodera O, Ikeuchi T, et al. Atrophy of the cerebellum and brainstem in dentatorubral pallidoluysian atrophy. Influence of CAG repeat size on MRI findings. Neurology 1997;49:1605-12.

12. Inazuki G, Baba K, Naito H. Electroencephalographic findings of hereditary dentatorubral-pallidoluysian atrophy (DRPLA). Jpn J Psychiatry Neurol 1989;43:213-20.

13. Saitoh S, Momoi MY, Yamagata T, Miyao M, Suwa K. Clinical and electroencephalographic findings in juvenile type DRPLA. Pediatr Neurol 1998;18:265-8.

14. Miyazaki M, Hashimoto T, Nakagawa R, et al. Characteristic evoked potentials in childhood-onset dentatorubral-pallidoluysian atrophy. Brain Dev 1996;18:389-93.

15. Kasai K, Onuma T, Kato M, et al. Differences in evoked potential characteristics between DRPLA patients and patients with progressive myoclonic epilepsy: preliminary findings indicating usefulness for differential diagnosis. Epilepsy Res 1999;37:3-11.